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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,301	12/15/2003	Michael Graham Cordingley	9/270A	5463

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EXAMINER	
ISSAC, ROY P	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/736,301	CORDINGLEY, MICHAEL GRAHAM	
	Examiner	Art Unit	
	Roy P. Issac	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6 and 8-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6, 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 2/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application claims priority under 35 U.S.C § 119(e) from provisional application 60/433,690 filed 12/16/2002.

This Office Action is in response to Applicant's amendment/ remarks/ response filed 2/07/2007 wherein claims 2-5, 7 and 11-15 have been cancelled, and claims 1 and 6 have been amended is acknowledged. Claims 1, 6 and 8-10 are currently pending.

Rejections Withdrawn

As indicated above, applicant's arguments/response filed 02/07/2007 cancelled claims 2-5, 7 and 11-15. All rejections and objections made with respect to the cancelled claims, 2-5, 7 and 11-15, in the previous office action are withdrawn.

The rejection under 35 USC 112 first paragraph, with respect to claims 1-3 in regards to the lack of enablement for any inhibitors of CYP450 is withdrawn, since applicants replaced the phrase "any inhibitors of CYP450" with "ritonavir" in claim 1.

The rejection under 35 USC 112 second paragraph, with respect to claims 6-15 in regards to the phrase "a human in need of such treatment" is withdrawn since said phrase is replaced with the phrase "treating HIV-1 infection in a human suffering from HIV-1 infection which method comprises co-administering to said human".

The rejection under 35 USC 112 second paragraph, with respect to claims 1-5 in regards to the missing phrase after "administering" is withdrawn since the phrase "to said human" is inserted.

The following are modified rejections necessitated by Applicant's amendment filed 2/07/2007, wherein the limitations in pending claims 1, 6 and 8-10 as amended now have been changed since claims 1 and 6 were amended, claims 2-5, 7, and 11-15 were cancelled. Claims 8-10 depend from amended claim 6. The limitations in the all claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, filed 08/08/2006, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 6 and 8-10 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Simoneau B et. al (U.S. Patent No. 6,420,359; Of Record) in view of Malaty et. al.(Of Record)

The '359 patent is drawn to the use of the compound of formula I for the treatment of HIV infection. (Claims 1-3, 5 and 8-9; Columns 41-44). The '359 application further discloses the compound of formula I as a non-nucleoside reverse transcriptase inhibitor (NNRTI). (Column 2, lines 30-35). The '359 patent further

discloses the use of compound of formula I in the range of 0.1mg -800 mg per day for a patient weighing 70 kg. (Column 4, last paragraph to Column 1, first paragraph).

The '359 patent does not expressly disclose the co-administration of ritonavir with the compound of formula I, or the use of ritonavir in the claimed dosage range to achieve a reduction in the rate of metabolism of the compound of formula I.

Malaty et. al. teaches that ritonavir is a potent inhibitor of Cytochrome 450 enzyme (CYP 450) and its isozymes, including CYP3A4. (Page 148, Colum1, last paragraph and Column 2, first paragraph). Malaty teaches that ritonavir slowed the rate of metabolism of two non nucleoside reverse transcriptase inhibitors, delaviridine and efavirenz. (Page 154, Column 2, Section titled Reverse Transcriptase Inhibitors). The rate of availability of the drug measured by AUC measurement showed a 21% increase for Efavirenz in combination with ritonavir. (Page 154, Column 2, Section titled Reverse Transcriptase Inhibitors). Malaty teaches that ritonavir reduces the metabolism, and thus increases the plasma concentration of at least 10 other HIV drugs. (Page 165, Table VII). In case of indinavir, the rate of plasma conecentration, measure by AUC, was increased by 475%. (Page 164, Column 1, Paragraph 2, lines 5-10). Malaty et. al. further teaches dosage regimens of ritonavir in 300 mg, 400 mg 500 mg and 600 mg dosage units. (Page 150, Column 2, last paragraph to Page 151, Column 1, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to co-administer ritonavir with the compound of formula I to reduce

its rate of metabolism, because ritonavir was well known for its inhibition of the CYP 450 enzyme and its effectiveness in increasing the plasma concentration of HIV drugs.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine ritonavir with the Compound of formula I to slow its metabolism because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection.

One of ordinary skill in the art at the time the invention was made would have been motivated to co-administer ritonavir with the Compound of formula I to slow down the metabolism of said compound because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection. The claimed ranges of ritonavir (about 30 mg to 1000 mg) and the compound of formula I (50 –6750 mg) overlaps with the dosages disclosed in the '359 patent for said compound (0.1-800mg) and that disclosed in Malaty et. al for ritonavir (300-600 mg). If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir 1990). See MPEP § 2144.05 [4-1].

Therefore one of ordinary skill in the art would have reasonably expected that combining a ritonavir with the compound of formula I, both known useful for treating HIV infection, would improve the therapeutic effects for treating the same disease, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third

composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1, 6 and 8-10 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Simoneau B, (WO 01/96338; Of Record) in view of Malaty et. al..(Of Record).

Simoneau B. discloses the use of the compound of formula I as an inhibitor of HIV-1 reverse transcriptase and as useful for the treatment of AIDS. (Page 7, Paragraph 2, lines 7-13). Simoneau patent further discloses the use of compound of formula I in the range of 0.1mg -800 mg per day for a patient weighing 70 kg. (Page 7, Paragraph 3, lines 19-25).

Simoneau does not expressly disclose the co-administration of ritonavir with the compound of formula I, or the use of ritonavir in the claimed dosage range to achieve a reduction in the rate of metabolism of the compound of formula I.

The disclosure of Malaty et. al. is dicussed above.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine ritonavir with the Compound of formula I to slow its

metabolism because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection.

One of ordinary skill in the art at the time the invention was made would have been motivated to co-administer ritonavir with the Compound of formula I to slow down the metabolism of said compound because ritonavir is a potent inhibitor cytochrome 450 enzyme and ritonavir is well known to slow the metabolism of inhibitors of HIV infection. The claimed ranges of ritonavir (about 30 mg to 1000 mg) and the compound of formula I (50 –6750 mg) overlaps with the dosages disclosed by Simoneau for said compound (0.1-800mg) and that disclosed in Malaty et. al for ritonavir (300-600 mg). If the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie* case of obviousness exits. See *In re Woodruff,* 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir 1990). See MPEP § 2144.05 [4-1].

Therefore one of ordinary skill in the art would have reasonably expected that combining a ritonavir with the compound of formula I, both known useful for treating HIV infection, would improve the therapeutic effects for treating the same disease, and/or would produce additive therapeutic effects in treating the same.

It has been held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Response to Arguments

Applicant's arguments and additional references cited therein, filed 2/07/2007, with respect to the above rejections under 103(a) have been fully considered but they are not persuasive

Applicants argue that it was not known that the compound of Formula I was metabolized by CYP450, and thus would not have provided the motivation to one of ordinary skill in the art to use ritonavir to improve the pharmacokinetics of the compound of Formula I. This argument was found unpersuasive since one of ordinary skill in the art would have found motivation to combine compound of Formula I with ritonavir because both compounds were known to be useful for the same purpose, to treat HIV. As indicated in the previous office action, citing *In re Kerkhoven*, it has been held that it is prima facie obvious to combine two compositions each of with is taught by the prior art to be useful for same purpose in order to form a third composition that would be used for the very same purpose.

Furthermore, the ability of ritonavir to inhibit CYP450 provides additional motivation to combine compound of Formula I with ritonavir. Applicant has indicated that prior to the instant invention it was not known that the compound of Formula I was metabolized by CYP450. However, Malaty et. al. teaches that all available proteases at the time were metabolized by CYP450. (Abstract). Since all known proteases, a large

group of compounds with diverse structures were metabolized by CYP450 one of ordinary skill in the art would have expected compound of Formula I to be metabolized by CYP450.

Applicants assert that the present invention resides in the discovery that the compound of formula I is subject to surprisingly rapid metabolism by the cytochrome P450 complex, and that the compound of formula I is so rapidly metabolized by said enzymes was previously unknown. However, the applicants have not compared the unexpected results to the rate of metabolism of any other compounds. To establish unexpected results over a claimed range, applicants should compare a sufficient number of tests both inside and outside the claimed range to show the criticality of the claimed range. *In re Hill*, 284 F.2d 955, 128 USPQ 197 (CCPA 1960). The applicants have made no such comparisons here. (MPEP 716.02). Malaty et. al. notes that protease inhibitors are metabolized in the liver by CYP P450 enzyme system especially the CYP3A4 isoenzyme. As such, one of ordinary skill in the art would have expected CYP450 to metabolize the compound of formula I as well. Here, applicants have not established any unexpected in the metabolism of the compound of formula I by CYP450. A surprisingly high rate of metabolism can only be made by comparison to the closest prior art, which the applicants have not made. As such, the rejections under 103(a) are still deemed proper and are adhered to.

No Claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Roy P. Issac whose telephone number is 571-272-2674. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

4/23/07

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